Breast Cancer Risk Factors Among Screening Program Participants [1]

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ABSTRACT—To examine whether the usual risk indicators for breast cancer apply to individuals participating in screening programs, data were obtained by mailed questionnaire from 405 breast cancer patients identified during the first 2 years of operation of the Breast Cancer Detection Demonstration Project and from a sample of 1,156 normal screenees (response rate = 88%). Nearly all of the recognized risk factors were seen in this population. The relative risk (RR) of breast cancer was 3.9 among women whose mothers were also affected ($P<0.01$). In addition, the relative risk was increased for women reporting early menarche, late menopause, nulliparity, late age when first child was born, and excessive weight. The relative risk was not elevated in women with a prior breast biopsy (RR = 0.8) but was excessive for those with more than one biopsy (RR = 2.0). No association with thyroid medications or menopausal hormones was found. Among women having undergone a natural menopause, a nonstatistically significant elevation in the relative risk was noted for long-term users (≥5 yr) of oral contraceptives; such an excess was not seen among premenopausal women or those having a surgical menopause. Among women with natural menopause, the excess relative risk was restricted to those using birth control pills in the presence of breast cancer risk indicators, i.e., a history of previous breast biopsy, family history of breast cancer, and late age when first child was born. Although based on small numbers, the results indicate the need for further study of women with extended periods of oral contraceptive use, particularly when accompanied by other known risk indicators.—J Natl Cancer Inst 62: 37-43, 1979.

Although periodic screening for the early detection of breast cancer may also provide an opportunity for epidemiologic inquiries into the etiology of this disease, the selected nature of women who attend these clinics must be considered. We undertook the present study to evaluate the potential of screening programs for the examination of etiologic hypotheses by determining whether the known risk indicators for breast cancer apply to the participating women. For this purpose we obtained information from volunteers in a large on-going screening program—the BCDDP. The data also enabled a preliminary evaluation of several "speculative" risk indicators for breast cancer, including use of hormones during menopause and use of oral contraceptives.

METHODS

Subjects were selected from 80,000 women enrolled during the first 2 years of screening in the BCDDP, jointly sponsored by the American Cancer Society and the National Cancer Institute. Screening began at the various project sites between mid-1973 and mid-1975. Asymptomatic women, 35 years of age or older, were recruited for annual screening over a 5-year period, with each screen consisting of physical examination, mammography, and thermography.

During the first 2 years of screening in the 18 largest screening centers (*see* the acknowledgments for locations, footnote 6), 543 new cases of breast cancer were detected. Although these cases were histologically diagnosed by a hospital pathologist, a pathologic review of the entire series had not yet been undertaken. Attempts were made to group-match these patients with three times as many normal screenees, stratifying on eight 5-year age groups, four races, 18 screening

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ABBREVIATIONS USED: BCDDP = Breast Cancer Detection Demonstration Project(s); CI = confidence interval(s); RR = relative risk(s).

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centers, and four 6-month intervals of entry into the project. The stratification scheme did not allow exactly three times as many controls as breast cancer patients to be derived; 1,422 controls satisfied the stratification criteria.

From information obtained at the initial screening examination, the following data were abstracted for each patient: age, race, marital status, family history of breast cancer, prior history of breast surgery, place of birth, family income, education of patient and spouse, height, and weight. A mailed questionnaire was sent to each subject to elicit more data on reproductive and medical histories; on use of birth control pills and other female hormones; and on use of drugs for diabetes, hypertension, edema, and thyroid conditions.

The measure of strength of an association used in these analyses is the relative risk, approximated by the relative odds (*1*). The relative risk is a measure of the risk of disease among those having a particular exposure compared to those not exposed. A relative risk of 1.0 would indicate no difference in risk between those exposed and those unexposed. A relative risk of 2.0 would indicate that the exposed patients had a risk of the disease twice that for those not exposed. For variables with multiple levels of exposure, risk was compared to an arbitrary base line of the first exposure level. When the analyses were controlled for the influence of other variables, the estimate of relative risk was the maximum likelihood estimate obtained after stratification of the data on various levels of the control variable (*2*). Asymptotic 95% CI were calculated for the estimates of relative risk (*2, 3*). When the 95% CI did not include 1.0, the relative risk was statistically significant at the $P<0.05$ level. In instances of multiple naturally ordered levels of exposure to a factor, the trends in the estimates of relative risks by level of exposure were tested by the χ^2 test for linear trend or its analog after stratification on a control variable (the Mantel extension of the Mantel-Haenszel procedure) (*4*).

The relationship of antihypertensives and diuretics to breast cancer risk in this study was previously reported (*5*).

RESULTS

The overall response rate to the questionnaire was 88% (breast cancer patients, 88%; controls, 89%). Of the women for whom questionnaire data were not obtained, 2% had died, 11% refused to respond, 3% moved without a forwarding address, and 84% failed to return the questionnaire.

No substantial differences were found between the respondents and the nonrespondents for the variables on which information had been obtained at the time of the initial screening. A slightly higher percentage of respondents than nonrespondents were well educated and in the higher family-income brackets. In addition, a slightly higher percentage of respondents than nonrespondents had prior breast surgery. Essentially no differences were found among the 2 groups with regard to marital status, religion, family history of breast cancer, and height or weight.

Because most of the individuals participating in the BCDDP were white, the present analysis was restricted to the 405 cases of breast cancer detected among white women (91.4% of the total respondents) and to the 1,156 white controls.

The breast cancer patients and controls were not found to differ significantly in regard to age or center, which indicated the effectiveness of the stratification scheme for these variables. The proportions of women less than 50, 50–59, and 60 years of age or older were, respectively, 33.3%, 39.2%, and 27.4% for patients and 36.3%, 35.5%, and 28.0% for controls. There was, however, some relaxation on stratification for time of entry into the screening program, with 81.7% of the patients having entered the screening programs during their first year, compared with 70.1% of the controls ($P<0.01$).

Table 1 shows the distribution of selected demographic and socioeconomic variables for the breast cancer patients and controls. A higher proportion of the patients were single, separated or divorced, or widowed; these differences were not explained by differ-

TABLE 1.—*Demographic and socioeconomic variables for breast cancer patients and controls*

Demographic and socioeconomic variables	Breast cancer patients[a]		Controls[b]	
	Percent	Median	Percent	Median
Marital status				
Single	4.7		3.8	
Currently married	70.6		79.9	
Separated or divorced	7.9		5.3	
Widowed	16.8		11.0	
Religion				
Catholic	18.0		20.3	
Jewish	10.9		12.9	
Protestant	58.5		60.4	
Other	6.2		4.6	
None	6.2		1.4	
Unknown	0.2		0.4	
Family income,[c] $				
<10,000	20.3		19.4	
10,000–14,999	27.6		27.1	
15,000–29,999	38.8		37.8	
≥30,000	9.4		11.0	
Unknown	3.8		4.8	
Patient education, yr		12		12
1–8	6.9		6.7	
9–11	5.7		8.1	
12	34.1		45.0	
≥13	30.6		37.6	
Unknown	22.7		2.6	
Spouse's education, yr		13		12
1–8	7.2		8.0	
9–11	7.7		8.5	
12	16.3		30.4	
≥13	33.1		38.7	
Unknown	35.8		14.5	

[a] $n=405$.
[b] $n=1,156$.
[c] Among currently married women only: breast cancer patients, $n=286$; controls, $n=924$.

ences in parity between breast cancer patients and controls. No significant differences were apparent with regard to religion. Among the currently married women, there were essentially no differences in family income between the patients and controls. A slightly higher percentage of controls than patients reported education beyond high school, but a significantly higher proportion of patients had information missing on educational status.

Relative risks for several reproductive variables are presented in table 2. The risk of breast cancer was inversely related to the age at menarche: Women having first menstrual periods at the age of 14 years or older showed approximately a 20% lower risk compared to those having menarche under 12 years of age. Parous women had a lower risk than nulliparous women, and risk generally decreased with increasing parity. The association with parity, however, was explained by the age at which a woman delivered her first child (age at first birth), which was highly correlated with parity. Among the parous women, risk increased with age at first birth, a trend that was statistically significant. Women with first births at ages 20–24 and 25–29 had about 40 and 50% higher risk, respectively, than did women with a first birth at less than 20 years of age; women with a first birth at 30 years or more demonstrated a twofold excess risk. For women with a first birth before the age of 30 years, the risk was lower than for women never having given birth. However, the protection associated with the birth of a child was not seen for women who delayed their first birth until the age of 30 years or older. These women had approximately a 50% higher risk of breast cancer than did the nulliparous women.

Risk did not differ substantially between women with surgical menopause before the age of 45 years and women with natural menopause at the ages of 45–49 (table 3). However, women with a surgical menopause at ages 45–49 years were at a significantly increased risk relative to women with natural menopause at the same ages. The risks were similar for surgical and natural menopause when the event occurred after the age of 50 years. For women having had either a natural or a surgical menopause, the relative risks tended to be highest for those with a late age at menopause, although no linear relationship was present. The risk was about 25% higher for women with a natural menopause at ages 50–54 years and twice as high for those with menopause at 55 years or over, compared to those with natural menopause at 45–49 years of age. The same trend applied to surgical menopause, with the risk for women who had their operations at 45 years or later being about twice that of women who had surgical menopause at less than 45 years of age.

With the inverse relationship of breast cancer risk to age at menarche and, in general, its direct relationship to age at menopause, the relative risk increased with the cumulative years of menstruation for women with natural menopause and for those with surgical menopause. Among the natural menopause group, women with 40 or more years of menstruation had more than twice the risk found for those with less than 30 years of menstrual activity. For those with a surgical menopause, 35 years or more of menstruation was associated with a twofold excess risk compared to the risk associated with 30 or less years of menstruation ($P<0.05$).

Family history of breast cancer was a statistically significant risk indicator (table 4). Women whose

TABLE 2.—*Breast cancer risk by selected variables regarding reproduction*

Reproduction variables	No. of breast cancer patients[a]	No. of controls[b]	RR[c]	95% CI
Age at menarche, yr				
<12	64	165	1.00[d]	—
12	110	291	0.97[d]	0.7–1.4
13	108	335	0.85[d]	0.6–1.2
≥14	113	345	0.82[d]	0.6–1.2
Age at first birth, yr				
<20	26	116	1.00[e]	—
20–24	133	423	1.37[e]	0.8–2.3
25–29	98	288	1.53[e]	0.9–2.6
≥30	76	134	2.15[e,f]	1.2–4.0

[a] $n=405$.
[b] $n=1,156$.
[c] Linear trends: Age at menarche, $P=0.20$; age at first birth, $P=0.001$. Unknowns were excluded from analysis.
[d] Adjusted for differences in age and menopause status.
[e] Adjusted for differences in age and parity.
[f] $P<0.05$.

TABLE 3.—*Breast cancer risk by age at natural or surgical menopause*

Type of and age at menopause	No. of breast cancer patients	No. of controls	RR[a]	95% CI
Surgical menopause				
<45	51	203	0.89	0.5–1.4
45–49	43	88	1.69[b]	1.0–2.8
≥50	16	40	1.42	0.7–2.9
Natural menopause				
<45	17	54	1.06	0.5–2.1
45–49	47	159	1.00	—
50–54	72	199	1.22	0.8–1.9
≥55	24	37	2.17[b]	1.1–4.2

[a] Natural menopause at ages 45–49 yr was used as a base line. Adjusted for differences in age. Unknowns were excluded from analysis.
[b] $P<0.05$.

TABLE 4.—*Breast cancer risk by family history of breast cancer*

Relatives with breast cancer	No. of breast cancer patients	No. of controls	RR[a]	95% CI
None	314	930	1.0	—
Mother only	33	26	3.88[b]	2.2–6.8
Grandmother only	18	11	4.82[b]	2.1–11.1
Both mother and grandmother	5	3	4.87[c]	1.0–26.1

[a] Adjusted for differences in age and menopause status. Unknowns were excluded from analysis.
[b] $P<0.01$.
[c] $P<0.05$.

TABLE 5.—*Breast cancer risk by medical history variables*

Medical history variables	No. of breast cancer patients[a]	No. of controls[b]	RR[c]	95% CI
Previous breast biopsy				
No	228	889	1.00[d]	—
1	35	167	0.83[d]	0.5–1.2
>1	30	57	2.05[d,e]	1.2–3.4
Weight, pounds				
<125	78	279	1.00[d]	—
125–134	77	231	1.16[d]	0.8–1.7
135–154	128	357	1.29[d]	0.9–1.8
≥155	113	269	1.51[d,e]	1.1–2.1
Height, inches				
<62	47	164	1.00[f]	—
62–63	117	313	1.35[f]	0.9–2.0
64–65	104	359	0.97[f]	0.6–1.5
≥66	128	304	1.25[f]	0.8–2.0

[a] $n=405$.
[b] $n=1,156$.
[c] Linear trend: Weight, $P<0.01$. Unknowns were excluded from analysis.
[d] Adjusted for differences in age and menopause status.
[e] $P<0.05$.
[f] Adjusted for differences in age, menopause status, and weight.

TABLE 6.—*Breast cancer risk by use of menopausal hormones among women having natural menopause*

Menopausal hormone use category	No. of breast cancer patients[a]	No. of controls[b]	RR[c]	95% CI
Ever use				
No	82	223	1.00	—
Yes	78	225	0.97	0.7–1.4
Years of use				
<5	36	115	0.89	0.5–1.4
5–9	28	44	1.77	0.9–3.2
10–14	6	28	0.59	0.2–1.6
≥15	3	15	0.53	0.5–2.0
Years since initial use				
<5	15	61	0.65	0.3–1.3
5–9	33	58	1.62	0.9–2.8
10–14	9	43	0.58	0.2–1.3
≥15	16	41	1.03	0.5–2.0

[a] $n=160$.
[b] $n=449$.
[c] Adjusted for differences in age. Unknowns were excluded from analysis.

mothers had breast cancer had nearly four times the risk of developing the same disease; for women whose grandmothers had breast cancer, the risk was elevated approximately fivefold. These estimates were not substantially altered by adjustment for age at menarche, age at first birth, age at menopause, presence of prior breast surgery, or weight.

A previous breast biopsy (indicative of a prior history of benign breast disease) was not associated with an increased risk of breast cancer (RR = 0.8; table 5). This was not altered by controlling for year of biopsy, age at first birth, family history of cancer, age at menopause, or weight. However, women who had more than one previous breast biopsy had a twofold increased risk of breast cancer.

The relative risk of breast cancer was found to increase with weight (table 5); this linear trend was statistically significant. The risk of breast cancer was 1.3 for women weighing 135–154 pounds compared to women weighing less than 125 pounds and increased to 1.5 for women weighing 155 pounds or more. Initially there appeared to be an effect related to being tall (66 inches or more). Adjustment for weight, however, weakened this association, with the relative risk decreasing from 1.5 to 1.2.

When risk factors were examined according to age at onset of breast cancer (<50, 50–59, ≥60), no substantial variation was noted except for the difference between older and younger patients with a family history of breast cancer. A history of breast cancer in a mother or grandmother was associated with about a sixfold excess risk among patients under the age of 50 years, as compared to a threefold to fourfold relative risk for patients with a later onset of cancer. Thus the relative risk and consequently the proportion of disease among patients with a family history that could be attributed to this risk indicator were greater among the young

TABLE 7.—*Breast cancer risk by prior use of birth control pills among premenopausal women and women having natural menopause*

Birth control pill use category	Premenopausal women				Women having natural menopause			
	No. of breast cancer patients[a]	No. of controls[b]	RR[c]	95% CI	No. of breast cancer patients[d]	No. of controls[e]	RR[c]	95% CI
Ever use								
No	82	207	1.00	—	143	414	1.00	—
Yes	44	153	0.80	0.5–1.3	17	35	1.66	0.8–3.4
Years of use								
<5	21	80	0.72	0.4–1.3	11	24	1.53	0.6–3.5
≥5	22	62	0.97	0.5–1.8	6	11	1.79	0.5–5.6
Years since initial use								
<10	29	87	0.88	0.5–1.5	9	20	1.50	0.6–3.8
≥10	14	56	0.75	0.4–1.5	8	15	1.75	0.6–4.7

[a] $n=126$.
[b] $n=360$.
[c] Adjusted for differences in age. Unknowns were excluded from analysis.
[d] $n=160$.
[e] $n=449$.

than among the old. However, because the risk among those without a positive family history was so much lower in young women, our estimates of the actual number of cases per 100,000 attributable to this risk indicator was greater among older women.

In evaluation of the use of menopausal hormones, analyses were restricted to women who had undergone a natural menopause. Explicit information was not available on the type of surgical menopause (i.e., whether or not an oophorectomy was performed). This lack of detail was felt to confound an examination of use of exogenous hormones, inasmuch as oophorectomy is associated with a decreased risk of breast cancer but an increased likelihood of estrogen replacement. Among the women with natural menopause, the relative risk associated with having ever used hormones was 1.0 (table 6). In addition, there was no indication that risk increased with the years of use of menopausal hormones or with the period of time since initial use of such hormones. Adjustment for age at menarche, age at first birth, age at menopause, presence of prior breast surgery, family history of breast cancer, or weight did not alter the risk estimates associated with "ever use," "years of use," or "years since initial use" of menopausal hormones.

Among the women having natural menopause, those who previously used oral contraceptives experienced a relative risk of 1.7 compared to those who never did (table 7). The relative risk was 1.5 for women with usage of less than 5 years' duration and 1.8 for women whose usage was 5 or more years. Neither of these estimates was statistically significant at the 95% level. The risk was found to increase with years since initial use of the birth control pills. Among the women who had not yet undergone menopause, no significant excesses in risk were seen for "ever use," "years of use," or "years since initial use" of birth control pills.

TABLE 8.—*Breast cancer risk by prior use of birth control pills among women having surgical menopause*

Birth control pill use category	No. of breast cancer patients[a]	No. of controls[b]	RR[c]	95% CI
Ever use				
No	96	279	1.00	—
Yes	14	52	0.86	0.4–1.8
Years of use				
<5	9	40	0.68	0.3–1.6
≥5	4	12	1.18	0.3–4.4
Years since initial use				
<10	10	32	1.00	0.4–2.3
≥10	3	20	0.47	0.1–1.8

[a] $n=110$.
[b] $n=331$.
[c] Adjusted for differences in age. Unknowns were excluded from analysis.

The relative risk associated with "ever use" of birth control pills was not elevated among the surgical menopause group. Users of 5 or more years also did not demonstrate an increase in risk (table 8). There was no latent period effect according to years since initial use of the oral contraceptives among the women with surgical menopause.

The overall association of breast cancer with "ever use" of oral contraceptives and the increasing trend with years of use among the women with natural menopause were not confounded by age at menarche, age at first birth, age at menopause, presence of prior breast surgery, family history of breast cancer, or weight. In addition, risk estimates were not substantially altered by restriction of analysis to currently

TABLE 9.—*Breast cancer risk by prior use of birth control pills in association with selected breast cancer risk factors among women having natural menopause*

Factors	No. of breast cancer patients[a]	No. of controls[b]	Years of use: <5 RR[c]	<5 No. of exposed patients	≥5 RR[c]	≥5 No. of exposed patients	Total RR[c]	Total 95% CI
Previous breast biopsy								
No	93	355	0.95	5	1.02	3	1.00	0.4–2.6
Yes	26	80	5.02	3	16.03	2	7.03[d]	1.2–49.1
Family history of breast cancer[e]								
No	70	321	0.96	3	1.13	2	1.02	0.3–3.2
Yes	22	52	0.67	1	∞	3	2.64	0.4–18.0
Age at menopause								
<50	64	213	0.59	3	2.68	4	1.34	0.4–3.9
≥50	96	236	2.92	8	0.89	2	2.04	0.7–5.6
Age at first birth								
<23	32	111	0.47	1	0.66	1	0.47	0.1–2.8
23–26	33	117	1.21	3	1.21	1	1.69	0.4–7.5
≥27	56	137	2.57	6	3.70	4	3.09	0.9–10.0

[a] $n=160$.
[b] $n=449$.
[c] No previous use of birth control pills was used as base line. Adjusted for differences in age. Unknowns were excluded from analysis.
[d] $P<0.05$.
[e] Among either a mother, grandmother, sister, or daughter.

married women. Among the women having natural menopause, some interaction or a different association in the presence of other risk indicators was detected with several breast cancer risk indicators. Use of birth control pills showed a relative risk of 7.0 (95% CI, 1.2-49.1) for women with a prior breast biopsy (table 9); the risk was greater for those with more than one biopsy than for those with a single biopsy. In contrast, women without a biopsy had a risk of 1.0 (0.4-2.6). Among the women with a previous biopsy, risk increased with duration of oral contraceptive use, reaching a 16-fold excess risk for users of 5 or more years. These risk estimates were not affected by whether the use of birth control pills began before or after the initial biopsy. No association with birth control pill use was noted for women without a family history of breast cancer. However, nearly a threefold excess risk was associated with use of oral contraceptives in women with such a history; this relationship was attributable to an excessive risk among users of 5 or more years. Late age at first birth also seemed to enhance the relationship with use of oral contraceptives. A relative risk of 3.1 for first birth at age 27 years or older followed the "ever use" of oral contraceptives, with the risk increasing to nearly fourfold for users of 5 or more years. These interactions generally were not seen among the women who had undergone surgical menopause.

Diagnosis of thyroid conditions or use of medication for their treatment was not associated with a significantly increased risk of breast cancer. Relative risks (adjusted for age and menopause status) of 1.1 and 1.0 were calculated for a previous diagnosis and use of therapeutic agents, respectively. Although a high risk appeared to be associated with a previous diagnosis of diabetes (RR = 1.4), the risk dropped to 1.1 when adjustment was made for weight. Similarly, no association was seen for use of therapeutic preparations for diabetes (RR = 0.8).

DISCUSSION

The selective features of individuals participating in screening programs are well recognized. The BCDDP is no exception, in that the women who were recruited were highly self-selected for risk indicators for breast diseases. For example, nearly one-quarter of the participants reported a family history of breast cancer and about one-third had a first birth at or over the age of 27 years. The participants were also usually well educated; about one-third had attended college, compared to figures of about one-fifth derived from the U.S. census or from interviews of cancer patients (*6*).

Despite the selectivity of this group, most of the same risk indicators were demonstrated among these women as have been found in conventional studies of hospital-derived cases. The importance of ovarian factors in the etiology of breast cancer is indicated by the increase in risk associated with nulliparity, late age at first childbirth, early onset of menarche, and late age at menopause (*7*). These factors were all found to be related to breast cancer risk among the screenees. Parous women demonstrated a lower risk than did nulliparous women; among the parous women, risk generally decreased with the number of children. Parity, however, was only indirectly associated with breast cancer risk by means of its correlation with age at first birth. When age at first birth was examined, we found that women who had given birth before the age of 30 had a lower risk of breast cancer than did nulliparous women. In congruence with other findings (*8*), women who first became pregnant after the age of 30 years showed an excess risk compared to nulliparae. Such findings may result from a process whereby early pregnancy prevents tumor initiation and pregnancy after the age of 30 years causes promotion of previously transformed cells (*9*). Our study also indicated breast cancer risk to be inversely associated with age at menarche. This trend has been seen in many countries (*10*) but not consistently in the United States. In addition, years of menstruation appeared to be directly related to breast cancer risk among women with natural or surgical menopause. It was not possible to determine whether this association indicated an effect of total cyclic ovarian activity or whether susceptibility is influenced by the ages at which women experience menarche and menopause.

A number of health variables were found to be important risk indicators in our study. Most notable was a family history of breast cancer, especially among women with an affected mother or grandmother. Although the relative risk was higher among women whose grandmothers had breast cancer than among women whose mothers were affected, the estimates were not statistically different. The finding of an association between breast cancer and body weight was in accord with other studies (*11*, *12*). De Waard (*12*) reported that height and weight were independently related to breast cancer risk, but our study and a Canadian report (*13*) showed no clear association with height.

Several risk indicators that have been previously identified for breast cancer did not appear to influence risk among the screening participants. Risk was not associated with social class, as measured by either family income, patient education, or education of the spouse. Although the findings have not been consistent, several studies (*6*, *7*) have identified an increased risk for women of upper social class standing. In contrast to numerous reports (*14*, *15*), the present study did not demonstrate that surgical menopause at an early age confers protection relative to that from natural menopause at ages 45-49, and women with surgically induced menopause at ages 45-49 were actually at an increased risk compared to women having natural menopause at these same ages. Surgery at later ages may be associated with a low probability of an oophorectomy. It is also plausible that the perimenopausal symptoms that precipitated the surgery reflected a hormone imbalance. This hormone imbalance may be associated with a high risk of breast cancer, irrespective of surgery. Such hypotheses require evaluation with more precise information on details of surgery.

In our study, the risk of breast cancer was not related to prior breast biopsy despite numerous reports that benign breast disease predisposes women to breast can-

cer (*16–18*). An association was present if analysis was restricted to women having more than one biopsy. The rate for previous biopsy appeared to be excessively high among the participants in the screening program, including both the patients and the controls, with about 15% of the women reporting a history of at least one prior biopsy. Crude estimates from the National Health Survey (*19*) indicated that about 8% of the general population might have a biopsy by the age of 52 (the mean age of the subjects in the present study). Cole (*20*) has suggested that several types of benign breast disease may exist, not all of which are premalignant. The excessive history of prior biopsy, particularly a single biopsy, among volunteers in this program may be related to increased concern about smaller, less progressive lumps among these health-oriented women. If these conditions tend to include high proportions of benign disease without potential for progression to neoplasia, a true risk could have been diluted.

Because a substantial proportion of the study subjects reported previous use of oral contraceptives and/or estrogens for menopause, the effects of their use could be evaluated. Breast cancer was not associated with use of menopausal hormones. This is consistent with several case-control studies (*21, 22*) but contrasts with a recent prospective study (*23*) showing excess risk among persons followed 12 or more years after initial use of these agents. In that report, most women received replacement estrogens after oophorectomy, but in the present study only 40% of the menopausal women underwent surgical menopause and details of the operation performed are unknown. Discrepancies between ovarian status of patients and the proportion with extended time periods since initial use of hormones in the two studies may have contributed to the different findings. Use of oral contraceptives, however, did show some relationship to the occurrence of breast cancer among the women with a natural menopause, with risk increasing with duration of use. In addition, certain subgroups of users seemed to be especially prone to breast cancer. An excessive risk was seen among long-term users with a previous biopsy for benign breast disease; this finding agrees with that of Fasal and Paffenbarger (*24*). Oral contraceptives also seemed to enhance the effects of other risk indicators including family history of breast cancer and late age at first birth. Attempts were made to evaluate whether the risk associated with use of birth control pills was dependent on whether they were initially used before or after birth of the first child, but too few women had used them before childbirth. The effect of birth control pills applied primarily to women with a natural menopause and not to premenopausal women. Use of oral contraceptives among premenopausal women was actually associated with a decreased risk of breast cancer. These differences between the premenopausal women and those having undergone a natural menopause may partly reflect different causal factors for premenopausal and postmenopausal breast cancer (*25*).

The present analysis indicates that, with few exceptions, the classically recognized risk indicators for breast cancer occur among the select group of women volunteering for screening. We think this indicates the appropriateness of screening projects for epidemiologic studies to assess interactions between known risk indicators and to study the role of the "speculative" risk indicators (e.g., exogenous hormones) that have high exposure rates among these women. To assess such issues, large numbers of study subjects are mandatory. To meet these objectives, a large case-control study utilizing information obtained in home interviews from participants in the BCDDP is under way.

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